The Contribution of Regulatory Science to Personalized Medicine in Psychiatry

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--no conflicts of interest to disclose--

Disclaimer

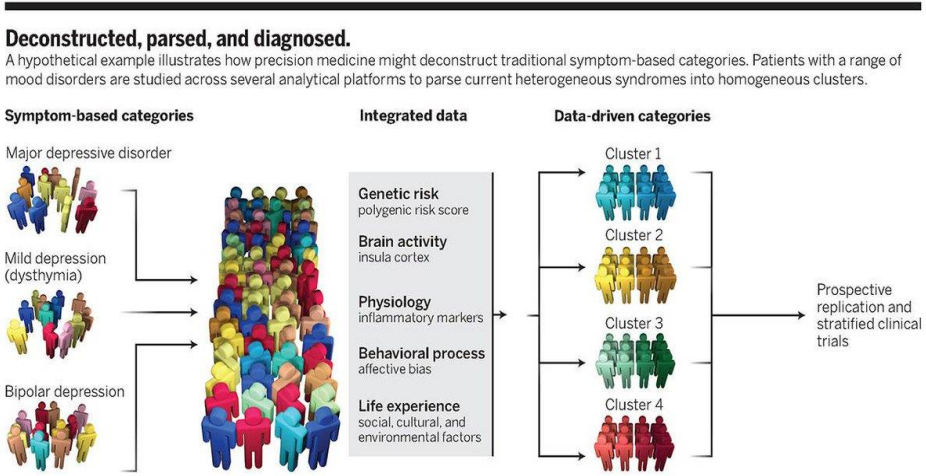
- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

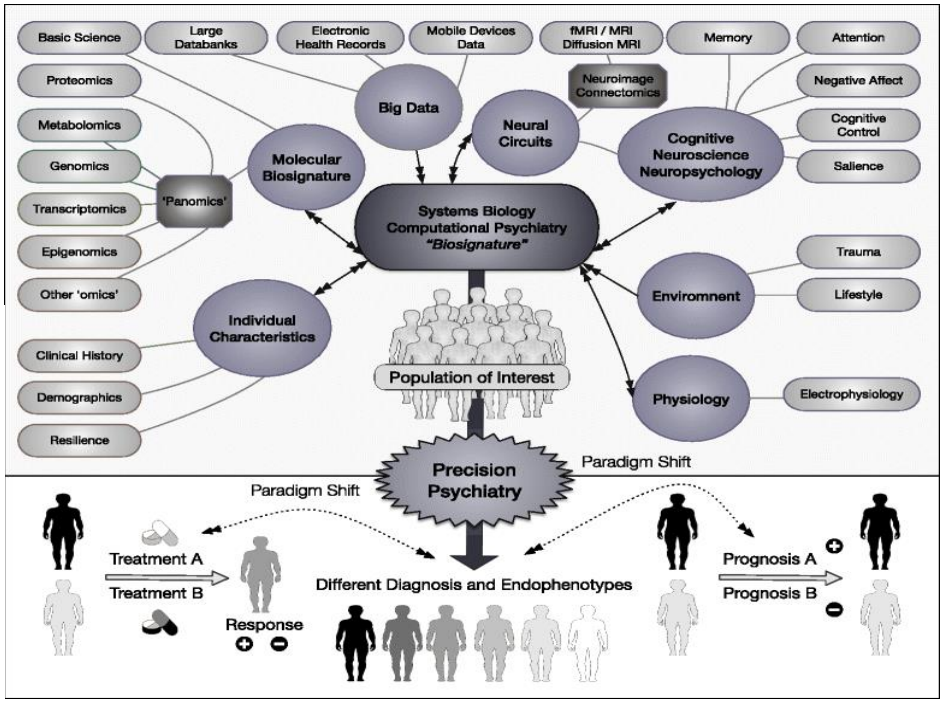
Towards Personalized Psychiatry

Roy Perlis	Awaiting the biomarker fairy: risk stratification in clinical trials
Ron Marcus	Adaptive Enrichment Designs: Modifying Pre-Specified Enrollment Criteria
Isaac Galatzer-Levy	The Application of Machine Learning to Advance Phenotyping Selection and Prediction of Treatment Response
Robert Gibbons	Assessment of Clinical Profiles and Outcomes in Personalized Medicine

An Unmet Need…

Precision Medicine and Precision Psychiatry





Fernandes et al., BMC Psychiatry, 2017

Danilo Bzdok & Andreas Meyer-Lindenberg, Biological Psychiatry, 2018

A Methodological Framework

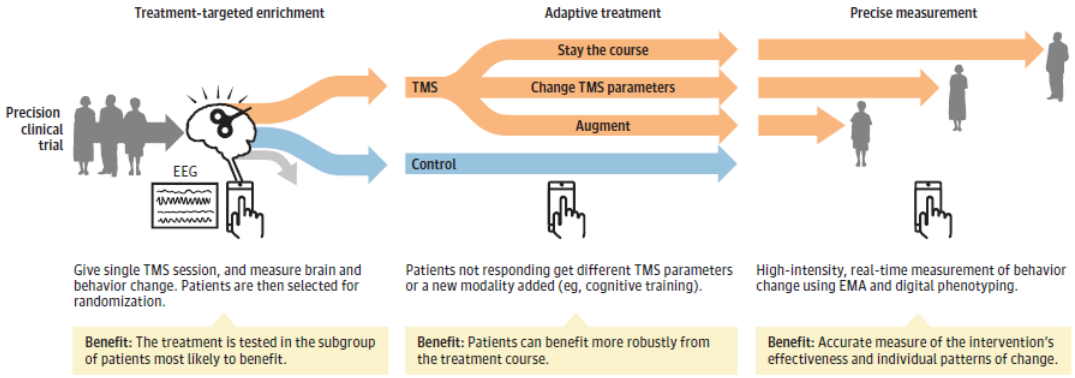
VIEWPOINT

A Framework for Advancing Precision Medicine in Clinical Trials for Mental Disorders

Precision Clinical Trials

- Treatment-Targeted Enrichment
- Adaptive Treatment
- Precision Measurement

Figure. Precision Clinical Trial Methods



Using the example of transcranial magnetic stimulation (TMS) for depression, this figure depicts the 3 features of precision clinical trials. EEG indicates electroencephalogram; EMA, ecological momentary assessment.

Eric J. Lenze JAMA Psychiatry July 2020 Volume 77, Number 7

Outline

The tools:

- Enrichment and Adaptive Enrichment
- Biomarker Framework
- Personalized Outcomes

Enrichment and Adaptive Enrichment

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (MARCH 2019)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products

Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry (DECEMBER 2019)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

"*These are potentially powerful strategies for the pharmaceutical industry because appropriate use of enrichment could result in smaller studies, shortened drug development times, and lower development costs*" Dr. Bob Temple

Enrichment strategies

Strategy to reduce non-drug related variability within a trial population

- Choosing baseline measurements reflective of a narrow range of severity
- Refined diagnostic inclusion criteria (gender)
- Placebo lead-ins in depression

Prognostic enrichment to select patients more likely to progress to detect an endpoint related signal

- Select patients more likely to develop dementia in the clinical trial timeframe (time to event)
- Requirement to have a recent exacerbation in MS clinical trials

Predictive enrichment to select patients most likely to respond to treatment

- A population of non-responders to a drug can be randomized to a new drug or the drug they did not respond to
- Responders are identified by a genetic or protein marker

Regulatory considerations

- FDA is very interested in targeting treatments to patients who can most benefit from them
- When enriching with empirical methods, results may or may not be generalizable
- The prescriber may/may not have a straightforward method to select patients for treatment
- Implications for labeling (to which patient population the results apply, not apply or groups for which effect is not known)
- If using predictive enrichment strategies the FDA encourages to study at least a small subset of biomarker negative subjects
- When enrichment depends on a test, its performance characteristics (sensitivity and specificity) should be evaluated

Adaptive Enrichment

Adaptive enrichment can be a useful clinical trial when there are uncertainties in the performance characteristics of a predictive or prognostic marker such as:

- Cut off values
- Proportion of marker positive
- Magnitude of treatment effect in biomarker positive

In adaptive enrichment designs sample size re-estimation is often necessary

Adaptation should be prospectively planned

Need for appropriate type I error rate control

Drug Development Tool Qualification

Qualification is a conclusion that within the stated **context of use**, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review

- Types of Tools:

Biomarker

Clinical Outcome Assessment (COA)

Animal Model

A glossary of terminology

Biomarker: a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers**. A biomarker is not an assessment of how an individual feels, functions, or survives (a COA)!**

- **susceptibility/risk biomarker** - A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.
- **diagnostic biomarker** — A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
- **monitoring biomarker** - A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.
- **prognostic biomarker** - A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.
- **predictive biomarker** - A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.
- **pharmacodynamic/response biomarker** - A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.
- **safety biomarker** - A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

What hampers biomarker development in psychiatry?

- Partial understanding of the neurobiological underpinnings of the diseases

- Research groups and/or large consortia had limited knowledge of regulatory pathways and requirements

- Industry may consider the regulatory outcome of developing biomarkers programs uncertain and is therefore unwilling to invest in them

However, biomarker development in psychiatry is gaining momentum…

Requestor	Biomarker	CoU	FDA Recommendation
FNIH Biomarkers Consortium Autism Biomarkers Consortium for Clinical Trials (ABC-CT)	N170 to Upright Faces	An brain-based EEG (N170 to human faces) diagnostic biomarker to enrich clinical trials by reduction of ASD-associated heterogeneity, as an enrichment/stratification biomarker for the core social communication symptoms of ASD.	LoI accepted
Foundation for the National Institutes of Health Autism Biomarkers Consortium for Clinical Trials (FNIH ABC-CT)	Oculomotor Index of Gaze to Human Faces	An eye-tracking (the Oculomotor Index of Gaze to Human Faces) diagnostic biomarker to be used with clinical and demographic characteristics to select a less heterogeneous subgroup within subjects with autism spectrum disorder (ASD) for clinical trial enrichment.	LoI accepted
Yale University	Individualized Risk Calculator for Psychosis (IRC-P)	Prognostic biomarker intended for use in clinical trials to enrich for individuals most likely to progress to full psychosis and poor long-term functional outcomes. It will be used in conjunction with clinical high-risk for psychosis (CHR-P) or Attenuated Psychosis Syndrome (APS) diagnosis in young people aged 15-35 years of age	LoI accepted

Come to discuss with the FDA

Context of Use (COU):

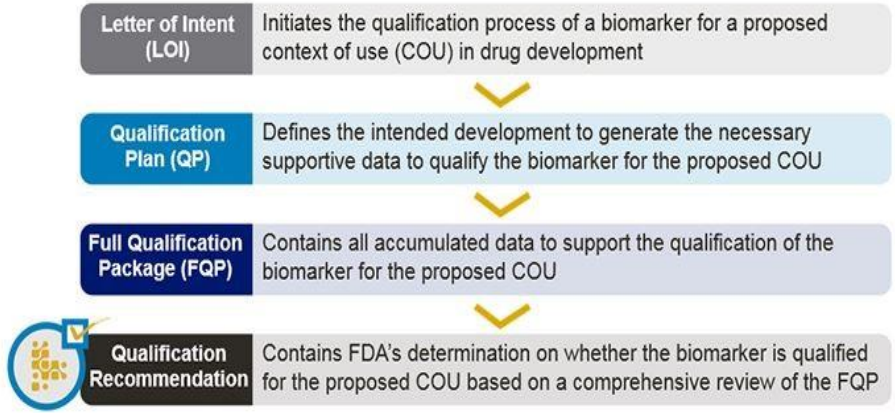
1) BEST biomarker category and
2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address?

o Inclusion/exclusion criteria for prognostic or predictive enrichment?
o Alter treatment allocation based on biomarker status?
o Result in adaptation of the clinical trial design?
o Establish proof of concept for patient population of interest?
o Support clinical dose selection for first in human or Phase 3 studies?
o Evaluate treatment response (e.g. pharmacodynamic effect)?
o Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?

- **IND Pathway -** in the context of a specific drug development program – discussion with the Division

- **DDT Qualification Program**:



ML/AI models

- ML/AI models could be used for enrichment
- FDA no experience so far with ML/AI models applied to drug development, therefore our considerations are theoretical
- ML/AI models are of particular interest in early drug development to integrate phenomenological and biological parameters.

- ML/AI models have been used to develop tools/devices for support in clinical decisions (e.g. select patients more likely to respond to one class of antidepressants)
  - How was the population selected to inform the model?
  - How much does it match with the clinical population for which it will be used?
  - Do we understand what the machine is doing and can we communicate it?
  - Interpretability/explainability of a ML model

ML = machine learning; AI = artificial intelligence

Personalized outcomes

- In a personalized COA approach the signs, symptoms, and functions assessed vary across patients in an effort to measure the most relevant outcomes for each individual (some personalized CoAs have a fixed “core” set of items)
- The concept of personalized COAs is still emerging and there are a number of challenges about their use in the context of drug development that need to be addressed
- Personalized COAs are advantageous in clinical settings (minimize clinician burden), however other considerations are necessary for their use in drug development
- Personalized COAs may measure discrete dimensions (fatigue) or multidimensional syndromes (depression). Unidimensional constructs may be more suitable as opposed to multidimensional constructs where a number of symptoms need to be assessed systematically

Personalized COAs: challenges

- Challenges in creating the item banks, all items must be relevant. Particularly in multinational trials when cultural factors may vary the relevance or language of the items.
- Challenges when training the algorithm on the weight attributed to each item
- It may be challenging comparing scores across patients because scores are attributable to a different set of items for each patient and item analyses are not possible
- Challenges when comparing scores longitudinally in time
- Logistic challenges for implementation large trials
- Potential advantages may lay in the possibility to access the extremes of the distribution and overcome ceiling/floor effects of existing instruments (providing that there are sensitive items)

Conclusions

- There is an unmet need for personalized medicine in psychiatry and regulatory science provides methodological framework to translate research into advancements in drug development
- FDA supports clinical trial strategies to target treatments to patients who can most benefit from them
- The FDA offers a DDT Qualification program to inform the use of biomarkers and CoAs in drug development depending on their CoU

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